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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/642,440	08/14/2003	Eli Wallace	064804-0054	2454
20277 7590 09/10/2007 MCDERMOTT WILL & EMERY LLP 600 13TH STREET, N.W. WASHINGTON, DC 20005-3096			EXAMINER JARRELL, NOBLE E	
			ART UNIT 1624	PAPER NUMBER
			MAIL DATE 09/10/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/642,440	Applicant(s) WALLACE ET AL.	
	Examiner Noble Jarrell	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 May 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 13-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12, 25, 26-35 and 37-39 is/are rejected.
- 7) ☒ Claim(s) 36 and 40 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 August 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6/18/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of Application

1. The Amendment-After Non-Final rejection received 5/16/2007 is acknowledged. Each argument has been fully considered and reviewed.

Rejections / Objections Withdrawn

Response to Arguments

2. Applicant's arguments, see pages 18-19, arguments (a), (b), and (d) under 35 U.S.C. 112, second paragraph, filed 5/16/2007, with respect to the indefiniteness of claim 26, lack of antecedent basis of claims 26-35, and species of claim 36 outside the scope or claim 1 have been fully considered and are persuasive, and thus these rejections have been withdrawn.
3. Applicant's arguments, see page 19, 35 U.S.C. § 112, filed 5/16/2007, with respect to solvates not having adequate written description have been fully considered and are persuasive.
4. Applicant's arguments, see page 19, under heading 35 U.S.C. § 112, filed 5/16/2007, with respect to the rejection(s) of claim(s) 1-12 and 25-35 under 35 U.S.C. § 112, first paragraph have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the scope of the claims.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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6. Claims 1-12, 25-35, and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preparation of compounds 1-48, does not reasonably provide enablement for compounds of claim 1 where variable n equals zero. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants adequately show the preparation of compounds 1-48 in the specification. Several methods of obtaining the final product are shown in figures 1-5. In these examples, only the formation of an imine bond is shown. There are no examples of compounds of claim 1 where variable n equals one being formed in the reactions. The figures that pertain to reaction schemes of the elected invention make only compounds where $n=0$. The reactions involved are not shown how they can be adopted to make compounds having an alkylene, alkenylene, or alkynylene link. Additionally, the specification is not adequately enabled for the scope of quinazolines claimed which can have a variety of groups for variable R^3 . Starting material sources for the quinazolines depicted in the specification which can be attached to variable R^3 at three positions are not seen but are required. Specification is silent as to the availability of necessary reactants needed to prepare such ring systems or if they are all commercially available. Note *In re Howarth* 210 USPQ 689; *Ex parte Moersch* 104 USPQ 122 for the need to show starting material sources commensurate with the claims' scope.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature

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of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) *The nature of the invention and (2) the breadth of the claims:*

The compounds are 4-amino quinazolines substituted with a wide variety of imino-substituted azolidine rings that can be further fused. Given the scope of "Z" coupled with the myriad of substituents permitted at variables R^1 - R^3 results in billions of compounds covered by the claims' scope.

(3) *The state of the prior art and (4) the predictability or unpredictability of the art:*

Compounds of claim 1 are not known in the prior art much less for uses relied on herein. Shen et al. (*European Journal of Medicinal Chemistry*, 2007, 42, 81-86) report quantitative structure-activity relationship (QSAR) models of inhibitory action of quinazolines toward tyrosine kinase receptors: Figure 1 (page 84) shows the core structure used for testing. Shen et al. found that electron-donating groups as variable Y in figure 1 enhance the inhibitory activity, whereas when variable Y is an electron-withdrawing group (such as nitro), the inhibitory activity is deactivated.

(5) *The relative skill of those in the art:*

One of ordinary skill in the art is a chemist familiar with the synthetic methodologies shown in figures 1-5.

(6) *The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for preparation of compounds of formula I where variable R^3 is hydrogen or methoxy and variable n is zero.

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However, the specification does not provide guidance for compounds of claim 1 where $n=1$. Also, no actual test data has been presented for compounds 31-48 and only a range is reported (<1 nM to 50 nM) for these compounds. Testing was done on compounds with a select number of groups variables R^1 , R^2 , and R^3 . Variable R^1 is an aryl group, however applicants only tested compounds where it is benzene. Variable R^2 is hydrogen or C_{1-8} alkyl, but applicants only tested compounds where it is hydrogen. Variable R^3 can be hydrogen, halogen, cyano, nitro, alkyl (saturated or unsaturated), any cyclic group, sulfonyl, an aldehyde, an oxo group, a carboxy group, amino, and 7 other groups. Since this invention is pharmaceutical in nature (it treats hyperproliferative disorders by inhibiting tyrosine kinase receptors), it in turn requires structure-activity relationship (SAR) data to determine if and what type of structural modifications to the basic structure will affect the binding site while retaining cytotoxicity. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiologically activity is generally considered to be unpredictable. See *In re Fisher* (166 USPQ 18).

(8) The quantity of experimentation necessary.

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-12, 25, and 37-39 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Rejections / Objections Maintained

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting

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rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-12 and 25-36 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 10, 20-91, and 101-106 of copending Application No. 10/914974 (Pregrant publication No. US 2005/0043334 A1 or PP'334). Although the conflicting claims are not identical, they are not patentably distinct from each other because instantly claimed formula I overlaps with formula I of PP'334 when there variables represent the following:

- i. A is Z (or $(U)_nZ$; $n=0$)
- ii. X is N;
- iii. R^1 is a substituted or unsubstituted, monocyclic or bicyclic, aryl moiety;
- iv. R^2 is H or a substituted or unsubstituted C_{1-8} alkyl;
- v. Z is the 5-membered ring having N, V, and W single/double bonded to N;
- vi. V is CR^7R^8 or CR^8R^9 .

Species in claims 101-106 of PP'334 also anticipate the instantly claimed formula I, and are analogous to some species recited in instant claim 36. Species in the instant claim 36 also anticipate formula I of PP'334.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed 5/16/2007 have been fully considered but they are not persuasive. The obviousness-type double patenting rejection is maintained because avoidance of literal overlap is not enough. Note that to preclude an obviousness-type double patenting rejection, claims must define an invention that is patentably distinct from claims in a copending application or parent. Note that H vs Me on nitrogens is not deemed a patentable advance absent evidence of superior, unexpected results. See *Ex parte Weston* 121 USPQ 428 and *In re Doebe/* 174 USPQ 158 regarding H vs. alkyl on nitrogen. Thus it would have been obvious to one skilled in the art at the time the invention was made to expect compounds claimed herein that are methylated on the NR⁶ nitrogen to also possess the uses taught by the art in view of the close structural similarity outlined above.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Applicant's arguments filed 5/16/2007 have been fully considered but they are not persuasive. The non-final action rejected claim 1 because applicants are not enabled for the "R² is a C₁₋₈ alkyl having a terminal carbon atom bound to one or the ring atoms of R¹". Even though this limitation was removed from claim 1, claim 2 recites this very limitation. If applicants are not enabled for this possibility, claim 2 should be amended or removed from the instant claims.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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12. Applicant's arguments filed 5/16/2007 have been fully considered but they are not persuasive. Claims 26-35 still lack antecedent basis under 35 U.S.C. 112, second paragraph because it is unclear which NR⁶ of claim 1 is being referred to in the proviso. In the proviso for claim 1, it is stated, "provided that NR⁶ of Z is not NH." What NR⁶ is the proviso referring to? Is it the NR⁶ that is required to be on the ring, or is it the NR⁶ that is one possibility for variable W?

13. Claims 1-6, 9-12, and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the proviso for claim 1, it is stated, "provided that NR⁶ of Z is not NH." What NR⁶ is the proviso referring to? Is it the NR⁶ that is required to be on the ring, or is it the NR⁶ that is one possibility for variable W?

14. Claims 34-35 are rejected for the following reasons: How can Z be methyl when it is a ring (perhaps applicants meant to say R⁶ is methyl)? Since claim 34 fails to further limit claim 33, claim 35 is also objected to.

Claim Objections

15. Claims 1, 7, 8 are objected to because of the following informalities: Superscripts and subscripts are too small, and are hard to read. Appropriate correction is required.

Allowable Subject Matter

16. Claims 36 and 40 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. The following is a statement of reasons for the indication of allowable subject matter: the closest prior art is reported by Heyl (US 2583774, issued January 29, 1952, see HCAPlus record). Heyl reports three structures, each of which does not anticipate the claims because NR⁶ is NH, which is a proviso of claim 1 in the current set of claims.

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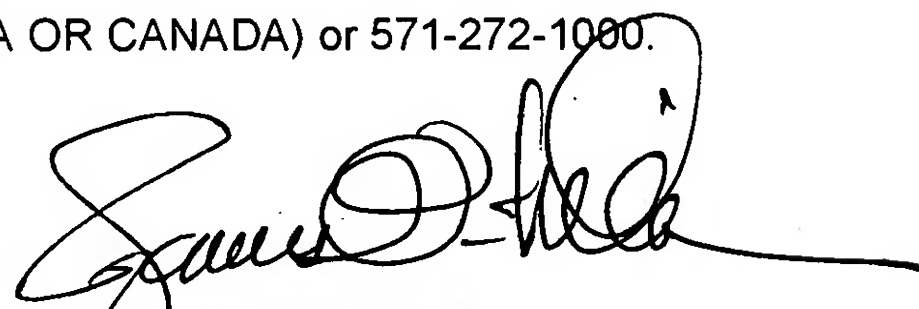
Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Noble Jarrell /NJ/



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